enhance the rate of target cell growth without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;

incubating the compound and the composition under conditions promoting cell growth; and

observing the cells for any effect not observed in cells not brought into contact with the composition.

Remarks

Rejections under 35 U.S.C. §112

The Examiner's very careful review of the specification and claims is greatly appreciated. The required corrections to the specifciation and claims have been made. A Letter to the Official Draftsman is enclosed with this Amendment. These amendments should moot the rejections under 35 U.S.C. §112

Rejections under 35 U.S.C. §102 or 103

Claims 1-9, 13, 19-25, and 31 were rejected under 35 U.S.C. §102(b) as disclosed by U.S. Patent No. 5,512,424 to Clapper, et al. Claims 1-9, 13-16, 18-25 and 31 were rejected under §103 as obvious over U.S. Patent No. 5,370,681 to Herweck, et al., in combiantion with U.S. Patent No. 5,171,264 to Merrill. Claims 10-12 and 26-28 were rejected under §103 as obvious over '264 Merrill in combination with Merrill, J. Biomater.

Sci. Polymer. 5, 1-11 (1993) or over Clapper et al. Claim 17 was rejected under §103 as obvious over Herweck et al., in combination with '264 Merrill in combination with U.S. Patent No. 5,522,895 to Mikos, et al. Claims 29 and 32 were rejected under §103 as obvious over Herweck, et al. in combination with '264 Merrill and U.S. Patent No. 5,032,508 to Naughton, et al. or over Herweck, et al., in combination with '264 Merrill and Tomomura, et al. J. Cell. Physiol. 30:221-227 (1987). These rejections are respectfully traversed if applied to the amended claims.

Amendments to the Claims

The claims have been amended to more clearly define the claimed invention as a substrate having bound thereto an effective concentration of growth factors to stimulate cell growth, wherein the growth factors are tethered to the substrate so that the cells are unable to internalize the growth factors (see page 5, lines 15-30, for example). Support for solid support is found, for example, at page 5, line 11; for polymeric tether, page 6, lines 23-26.

Clapper

Clapper (col. 6) describes the use of attachment factors to promote cell adhesion to a substrate, in order to culture adhesion- or attachment-dependent cells. These are not growth effector molecules, nor is there any disclosure of attachment via polymeric tethers in an amount effective to promote growth enhancement. Accordingly, Clapper does not disclose the elements defined by the amended claims.

Clapper also does not make obvious the claimed composition and method, since the only discussion is of the use of molecules which enhance **attachment**, not cell growth. See col. 6, lines 47-col. 7, line 23. It is important to read line 16 of col. 7 in context: "a sufficient density of cell adhesion factor should be carded by the bioreactor's supporting surface to promote cell attachment and growth"; this is not enhanced growth, but merely attachment-dependent growth, i.e., if the cells do not attach, they do not grow. See, for example, the discussion at col. 8, lines 54-67 and col. 10, lines 29-39.

Herweck, et al.

It is agreed that Herweck discloses an implantable device which can be coated with bioactive molecules. There is no teaching, however, that would lead one of skill in the art to make at a minimum the following alterations: select bioactive molecules **enhancing** growth rate and the amount required to enhance growth rate when not internalized and to chemically couple the molecules to the substrate in a density and with appropriate linkers to result in enhanced growth rates of attached cells.

Mikos, et al.

Mikos is similar to Herweck in that it is directed to a matrix for seeding with cells that can be implanted. It also does not disclose or make obvious selecting bioactive molecules **enhancing** growth rate, determining the amount required to enhance growth rate

when not internalized, and to chemically couple the molecules to the substrate in a density and with appropriate linkers to result in enhanced growth rates of attached cells.

Naughton, et al.

Naughton is actually quite similar to Clapper. It discloses a matrix which might be suitable for implantation, having attached thereto stromal cells that serve as attachment factors for other types of cells grown on the matrix. One skilled in the art would be led by the disclosure of Naughton to believe that no further modifications were necessary in order to grow cells since the stromal cells result in adequate cell attachment and growth.

In summary, the claims have been amended to more clearly define novel and non-obvious aspects of the claimed compostions and methods. None of the prior art provides the **motivation** to combine and modify the prior art disclosures as applicants have done, to achieve enhanced growth, nor would one of ordinary skill in the art have had any expectation of success in achieving **enhanced** growth, in the absence of actually conducting studies which demonstrate that one can obtain results beyond that obtained using the prior art methods, which involve the provision of attachment molecules directly on a substrate **or** molecules such as those of Merrill having the opposite effect - to repel (by virtue of the polyethylene oxide). See, for example, the results shown in Figure 2, where there is a significant difference achieved using the claimed modified substrates, as compared with the control where the growth effector molecule (EGF) is adsorbed to the surface.

Supplemental Information Disclosure Statement

Pursuant to the duty of disclosure under 37 C.F.R. §1.56, Applicants cite the following publications which were cited in the Search Report of the corresponding PCT application mailed July 31, 1996, copies of which are enclosed. Also enclosed is a check in the amount of $230.00 to cover the fee required for filing this Information Disclosure Statement. However, the Commissioner is authorized to charge Deposit Account No. 01-2507 if this fee is insufficient.

Foreign Document

Number	Date	County
0 531 733 A1	17/03/93	Europe
WO 89/05616	29/06/89	PCT
WO 91/01760	21/02/91	PCT
WO 94/28937	22/12/94	PCT
O 205 790 A2	30/12/86	Europe
4108377	9/04/92	Japan

Remarks

This statement should not be interpreted as a representation that an exhaustive search has been conducted or that no better art exits. Moreover, Applicants invite the Examiner to

make an independent evaluation of the cited art to determine its relevance to the subject matter of the present application. Applicants are of the opinion that their claims patentably distinguish over the art referred to herein, either alone or in combination.

Allowance of all claims 1-32, as amended, is earnestly solicited. A copy of all claims as pending after entry of this amendment is attached in an Appendix for the convenience of the Examiner.

Respectfully submitted,

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Dated: January 23, 1997
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404/873-8794

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this Amendment and Supplemental Information Disclosure Statement, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: January 23, 1997

Patrea L. Pabst

APPENDIX: Claims as pending after entry of the Amendment

1. A composition for stimulating the growth of eukaryotic cells comprising
a biocompatible solid substrate,
biocompatible synthetic polymeric tethers, and
growth effector molecules,
wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules.

2. The composition of claim 1 wherein the form of the biocompatible substrate is selected from the group consisting of netting, individual and woven fibers, sponge and shaped polymers.

3. The composition of claim 2 wherein the shape of the shaped polymer is selected from the group consisting of dishes, bottles, solid particles, hollow particles, and polymers shaped to match a desired tissue shape.

4. The composition of claim 1 wherein the biocompatible substrate is selected from the group consisting of glasses, metals and biocompatible polymers.

5. (amended) The composition of claim 4 wherein the polymer is selected from the group consisting of synthetic polymers and natural polymers.

6. (amended) The composition of claim 5 wherein the polymer is selected from the group consisting of proteins, polysaccharides, extracellular matrix proteins[;] , polyesters[;] , polycapralactone[;] , polyhydroxybutyrate[;] , polyanhydrides[;] , polyphosphazenes[;] , polyorthoesters, polyurethanes, and combinations thereof.

7. The composition of claim 1 wherein the tether is a water soluble, biocompatible polymer.

8. The composition of claim 7 wherein the tether is selected from the group consisting of polyethylene oxide, carboxymethylcellulose, and starch.

9. (amended) The composition of claim 1 wherein the growth effector molecules are selected from the group consisting of epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, and combinations thereof.

10. The composition of claim 1 wherein the tether has a backbone length between 5 and 50,000 atoms.

11. The composition of claim 10 wherein the tether has a backbone length between 100 and 50,000 atoms.

12. The composition of claim 10 wherein the tether has a backbone length between 5 and 500 atoms.

13. (amended) A method for growing eukaryotic cells comprising

bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules; and

maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow.

14. The method of claim 13 wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

18. The method of claim 13 wherein the form of the biocompatible substrate is selected from the group consisting of netting, individual and woven fibers, sponges and shaped polymers.

19. The method of claim 18 wherein the shape of the shaped polymer is selected from the group consisting of dishes, bottles, solid particles, hollow particles, and polymers shaped to match a desired tissue shape.

20. The method of claim 13 wherein the biocompatible substrate is selected from the group consisting of glasses and biocompatible polymers.

21. The method of claim 20 wherein the polymer is selected from the group consisting of synthetic polymers and natural polymers.

22. The method of claim 21 wherein the polymer is selected from the group consisting of polylactic acid, polyglycolic acid, polyanhydrides, polyorthoesters, collagen, glycosaminoglycans, polyamino acids, and combinations thereof.

23. The method of claim 13 wherein the tether is a water soluble, biocompatible polymer.

24. The method of claim 23 wherein the tether is selected from the group consisting of polyethylene oxide, carboxymethylcellulose, and starch.

25. (amended) The method of claim 13 wherein the growth effector molecules are selected from the group consisting of epidermal growth factor, platelet-derived growth factor, transforming growth factor, hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, extracellular matrix molecules, and combinations thereof.

26. The method of claim 13 wherein the tether has a backbone length between 5 and 50,000 atoms.

27. The method of claim 26 wherein the tether has a backbone length between 100 and 50,000 atoms.

28. The method of claim 13 wherein the tether has a backbone length between 5 and 500 atoms.

29. (amended) The method of claim 13 wherein the cells are selected [form] <u>from</u> the group consisting of parenchymal cells and stem cells.

30. The method of claim 29 wherein the cells are hepatocytes.

31. (amended) A cell culture comprising

a biocompatible <u>solid</u> substrate,

biocompatible <u>polymeric</u> tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether <u>so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules</u>, and wherein the growing cells are bound to the growth effector molecules.

32. (amended) A method of testing a compound for an effect on tissue comprising

bringing into contact the compound to be tested and a composition comprising

a biocompatible <u>solid</u> substrate,

biocompatible <u>polymeric</u> tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;

incubating the compound and the composition under conditions promoting cell growth; and

observing the cells for any effect not observed in cells not brought into contact with the composition.